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Rheological characterization of Microcrystalline Cellulose/Sodiumcarboxymethyl cellulose hydrogels using a controlled stress rheometer: part I

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Abstract

Rheological properties of two different commercial grades of Microcrystalline Cellulose/Sodiumcarboxymethyl Cellulose (MCC/NaCMC) hydrogels were investigated. A controlled stress rheometer fitted with parallel plate geometry was used. Application of the Cross Model relating the viscosity and shear rate data indicated the gels are extremely shear thinning. The two grades of Avicel (RC-591 and CL-611) made of varying MCC and NaCMC concentrations, exhibited distinguishable changes in yield stress and shear thinning behavior attributable to the individual composition. The hydrogels reached structural equilibrium in 1 week after manufacture. Lot to lot variability of Formula A hydrogels had minimal influence on the rheological properties of the resulting hydrogels. The yield stress and/or initial viscosity values observed were proportional to the concentration or phase volume of the MCC/NaCMC in water.

Keywords: Microcrystalline Cellulose; Oscillatory testing; Rheology; Shear thinning; Sodiumcarboxymethyl Cellulose; Structure build up and yield stress

1. Introduction

In the pharmaceutical industry, hydrogels are frequently used as suspending agents in liquid dosage forms, as adhesives in semisolid dosage forms and as modified release agents in solid dosage forms. Materials like carrageenan, gellan gum, xanthan gum and Microcrystalline Cellulose/Sodiumcarboxymethyl Cellu-

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lose (MCC/NaCMC) are such hydrogels that are frequently used. Though MCC/NaCMC gels are extensively used in the drug development process, very little is known about their thixotropic behavior and its significance in drug development.

The MCC/NaCMC (Avicel® RC-591, FMC) preparations are capable of forming highly stable thixotropic gels even at low concentrations (FMC). Avicel® RC-591 is a spray-dried blend of MCC and NaCMC. These gels have been studied by several investigators using conventional rheological techniques (Dolz-Planas et al., 1988, 1992; Dolz et al., 1991; Tamburic et al., 1996). All these studies were conducted using a Brookfield viscometer. These studies have established that the material under study is pseudoplastic and thixotropic but provided little insight into the evaluation of the thixotropy or structuring of these gels.

The current study was undertaken to better characterize the microstructure of hydrogels and their thixotropic behavior using a controlled stress rheometer. The theory and instrumentation for the controlled stress rheometry is presented elsewhere (Barnes, 2000).

2. Materials

Avicel® RC-591 (Microcrystalline Cellulose and Sodiumcarboxymethyl Cellulose,) USPNF Lots D017N, D022N (Formula A) and Avicel® CL-611 (Microcrystalline Cellulose and Sodiumcarboxymethyl Cellulose) USPNF Lot E042N (Formula B) are obtained from Newark, DE. Purified Water USP is used for hydrogel manufacture.

3. Equipment

The controlled stress rheometer (TA Instruments/AR 2000) is fitted with a 6.0 cm acrylic parallel plate. The parallel plate geometry is presented in Fig. 1. The shear constant (K_γ) using the parallel plate geometry is given by R/H (plate radius/plate gap). The shear rate γ (s^{-1}) is then obtained by $K_\gamma(\omega)$ (shear constant × angular velocity). The shear stress (σ) is the product of stress constant and torque ($K_\sigma \times M$). The stress constant (K_σ) which is dependent on the gravitational force and the plate geometry is given by $G_c/\pi(R/10)^3$.

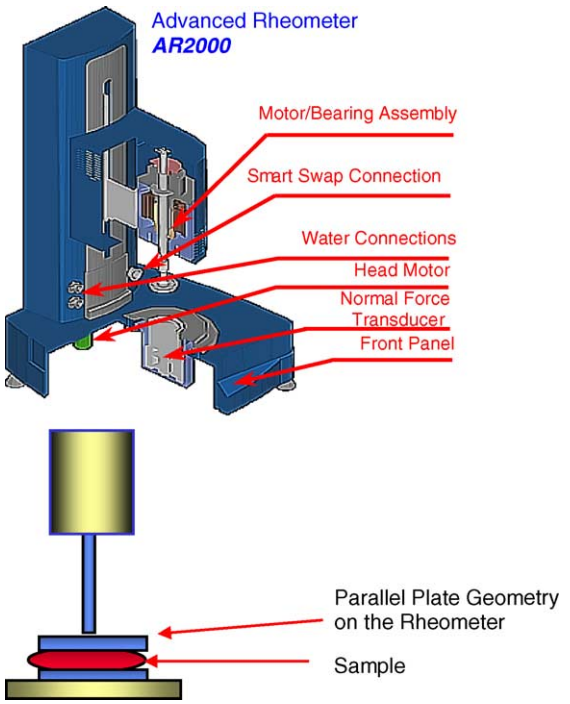

Fig. 1. Controlled stress rheometer (AR 2000) and parallel plate geometry used in the study.

4. Methods

4.1. Hydrogel preparation

The hydrogels were manufactured using the Silverson L4R homogenizer equipped with a general-purpose screen. The homogenizer is a high shear rotor/stator laboratory mixer which provides multi-stage mixing/shearing action as materials are drawn through the specially designed workhead and mixed.

Purified water was used as the vehicle for all the suspensions used in the study. Hydrogels were prepared at 1.0% w/w, 1.5% w/w and 2.0% w/w concentrations. The suspensions were then transferred to a 1 L high-density polyethylene bottle and were allowed to equilibrate for 1 week for complete structure formation.

5. Rheological studies

A TA instruments AR 2000 (Fig. 1) controlled stress rheometer was used for the study. Each gel sample was gently loaded onto the peltier plate using a tablespoon.

Care was taken to minimize shearing during sample removal and sample loading. All rheology studies were done at 20 °C unless specified otherwise.

Preliminary studies were conducted to optimize instrument parameters as well as to determine the length of time needed for complete gel structure formation. Once the system was optimized, three types of studies were conducted: shear thinning, peak hold and yield stress.

The shear thinning behavior of the samples was characterized over a range of 0–2500 s^{-1} for a period of 5 min. The resulting viscosity of the sample was recorded.

Peak hold studies were conducted by applying aconstant stress or shear to the sample under study over a specified period of time, and the resulting viscosity of the sample was mapped.

To determine the yield stress of the gels, the rheometer was programmed to apply a specified amount of shear stress on the sample over a set period of time and the resulting strain was recorded. This experiment was done over a range of shear stresses (0.1 to 10 or 25 Pa), and the resulting deformation was obtained.

6. Results and discussion

The elastic modulus (G') was used as the response variable during preliminary experimentation as it was the most sensitive parameter in viscoelastic measurements (Barnes, 2000).

The results indicate that the mode of gap closure did not significantly influence the sample characteristics (G') under the conditions tested. All future testing on the samples was conducted using exponential close to minimize sample shearing. Initial studies showed that at 1000 and 2000 μm plate gap samples exhibited smooth flow curves, whereas at 500 μm gap, an abrupt change in G' at around 10 Pa was observed which indicated shear fracture or wall slip. Therefore, for future experiments, the parallel plate gap was fixed at 1000 μm unless otherwise specified.

Preliminary studies also indicate that at a frequency of 5.0 Hz, the sample exhibited a higher threshold for the material to flow (greater critical stress) when compared to the data from 0.1, 1.0 and 2.0 Hz. A sample subjected to stress ramping at a lower frequency of 0.1 Hz (increased amplitude) exhibited erratic flow at high stress. Flow curves were smooth and uneventful at frequencies of 1.0 and 2.0 Hz. Based on the results, future samples were tested using 1.0 Hz frequency unless otherwise specified.

An additional study was conducted to determine the time required for the test gels to reach structural equilibrium after manufacture. Freshly prepared samples were left undisturbed for varying time periods. These samples were then subjected to continuous shear stress

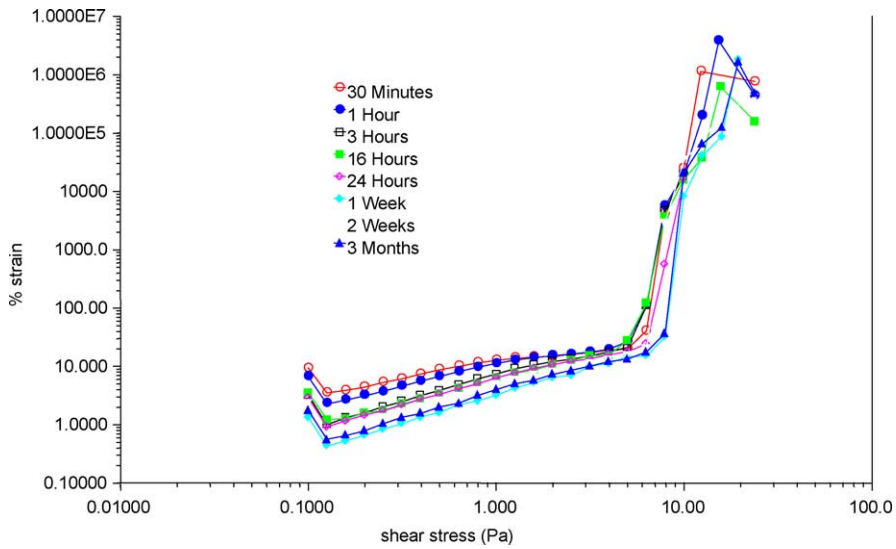

Fig. 2. Influence of storage time on the shear stress vs. strain relationship of MCC/NaCMC hydrogels (Formula A, 1.5% w/w).

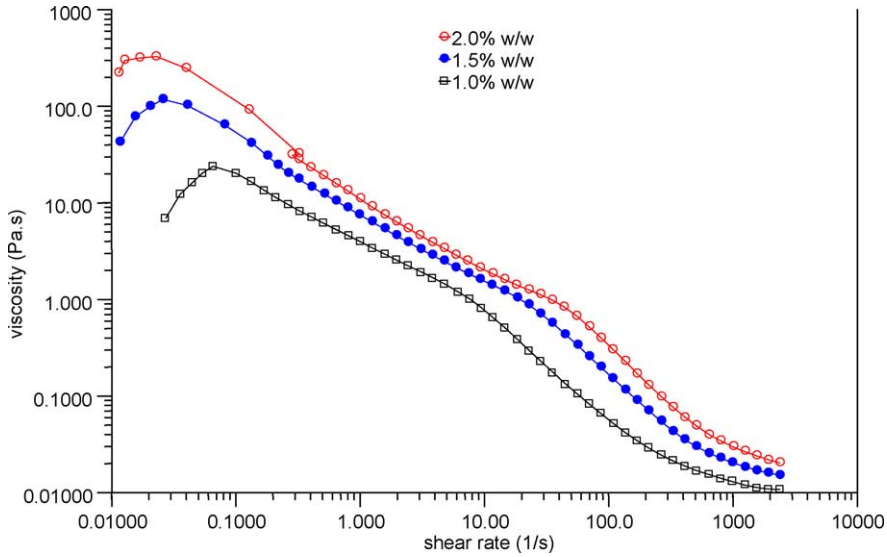

Fig. 3. Influence of shear rate on the viscosity of hydrogel (Formula A) at varying concentrations.

ramps and the resulting strain of the samples was monitored (Fig. 2).

The stress versus strain relationship was not linear for the samples resting for less than 24 h. This indicates the incomplete formation of gel structure because at low shear stresses depending on the gel elasticity, stress is directly proportional to the strain, and a straight line should be observed (Barnes, 1997, 2000). The shear

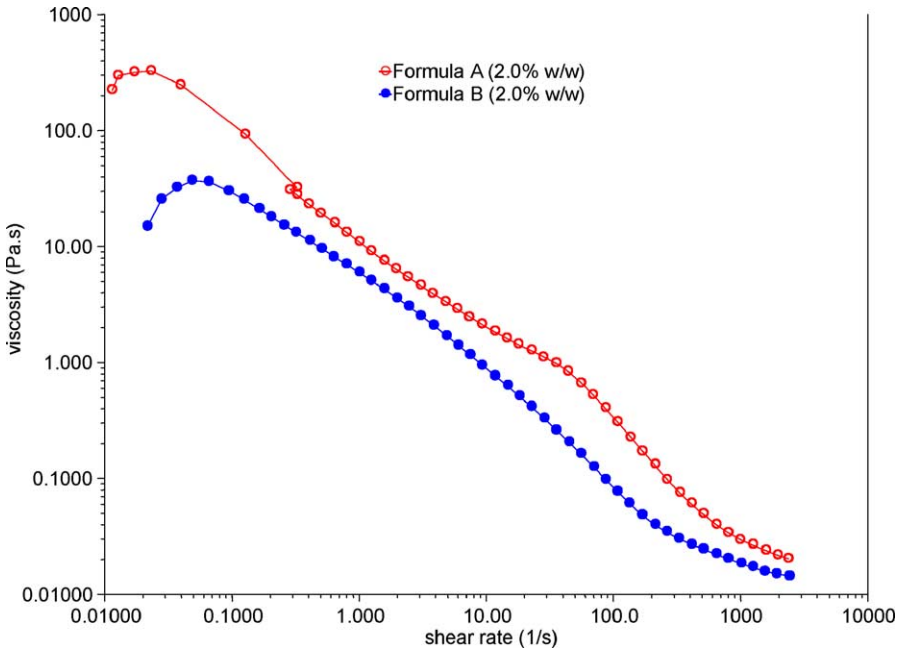

Fig. 4. Influence of shear rate on the viscosity of different grades of MCC/NaCMC hydrogels.

Table 1
Shear thinning of MCC/NaCMC hydrogels—application of cross model

Cross model parameter	MCC/NaCMC (Formula A) concentration		
	1.0% w/w	1.5% w/w	2.0% w/w
η_0 (zero shear viscosity, Pa s)	18.85	107.5	1450.0
m (rate index)	1.03	0.88	0.84

stress at which the material deviates from this behavior is called the yield stress and is a good indicator of structural integrity. The lack of complete structure formation was also supported by the lower yield stress (Pa) observed for gels at rest for less than 24 h.

After 1 week, the gels appear to have reached structural equilibrium as indicated by linear relationships observed between shear stress and strain. No rheological changes were observed after longer storage. Therefore, samples were allowed to equilibrate for a minimum of 1 week after manufacture before being used for further studies.

6.1. Shear thinning behavior of MCC/NaCMC hydrogels

MCC/NaCMC gels of varying concentrations were manufactured and characterized for their shear thinning behavior (Figs. 3 and 4). Various mathematical models (Barnes, 1997, 2000; Nielloud and Marti-Mestres, 2000; Stability of Dispersions, 2001) are used to explain the shear thinning behavior of hydrogels. Malcolm Cross (Barnes, 2000), an ICI rheologist found that most shear thinning liquids could be described by Eq. (1):

$$\frac{\eta - \eta_\infty}{\eta_0 - \eta_\infty} = \frac{1}{1 + (K \times \dot{\gamma})^m} \quad (1)$$

The Cross Model (Eq. (1)) describes the relation between viscosity and shear rate. The model includes four parameters: the low shear viscosity (η_0); the high shear viscosity (η_∞); K which has the units of time, and m, a shear index which is dimensionless. The degree of shear thinning is dictated by the value of m. When m approaches zero the liquid is Newtonian, while the most shear thinning liquids have a value of m approaching unity. Shear rate is used as the independent variable.

Application of the Cross Model to the three samples indicated that the gels were significantly shear thinning with 'm' tending to unity, and at low shear rates yield stress was observed. The yield stresses or initial viscosity values observed were proportional to the concentration or phase volume of the MCC/NaCMC in purified water (Table 1).

A different grade of 2.0% w/w MCC/NaCMC (Formula B) gel exhibited similar shear thinning behavior ($m = 0.99$) but significantly low initial viscosity of 37.22 Pa s when compared to the Formula A gel of similar composition. This may be due to the presence of a different grade of NaCMC and the lower concentration of MCC particles present in the material (FMC). Formula B at concentrations below 2.0% w/w did not form hydrogels.

The shear thinning behavior of these hydrogels can be classified into distinct flow regimes. Assuming the MCC particles are spherical (Fig. 5), at very low shear rates the material flow is classified as the first Newtonian plateau where the Brownian diffusion keeps microstructure random and viscosity is constant (material at rest). This is followed by the flow regime where hydrodynamic forces impose order, particles align along flow streamlines and viscosity decreases (material be-

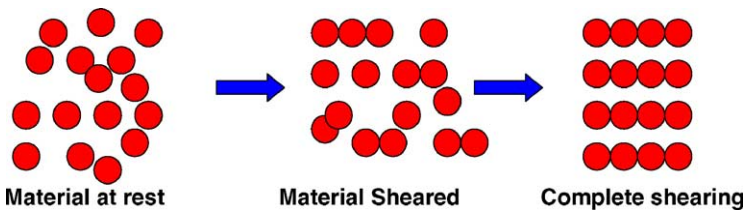

Fig. 5. Hydrodynamic ordering of MCC particles in hydrogels subjected to increased shear.

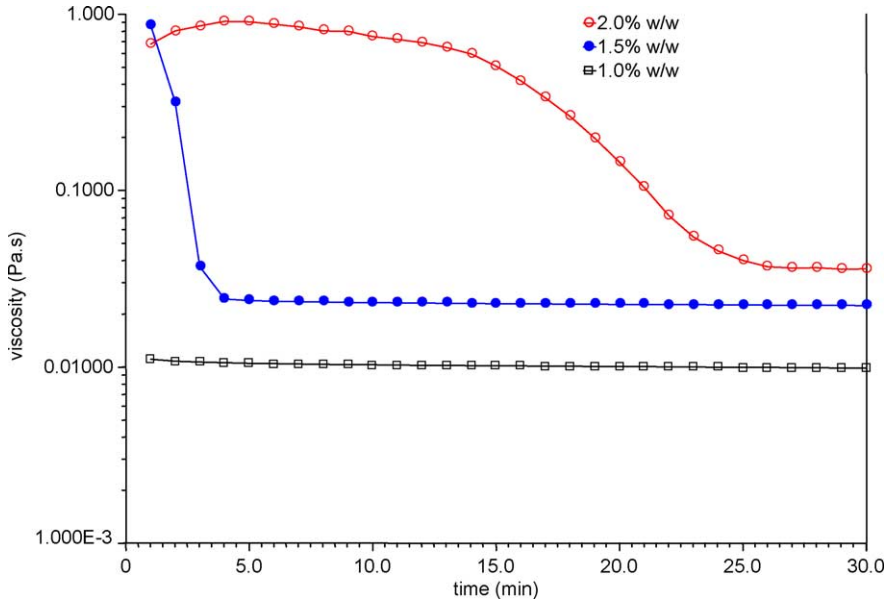

Fig. 6. Effect of constant shear stress (15 Pa) on the viscosity of MCC/NaCMC hydrogels (Formula A) of varying concentration over time.

ing sheared). This is then followed by flow regime (or the 2nd Newtonian regime) where maximum order is achieved and viscosity once again becomes constant (complete shearing) (Kutschmann).

At rest, the Brownian motion randomizes the particles, under shear the particles align along streamlines. Also, the increase in viscosity with increase in phase volume of particles may be due to the in-

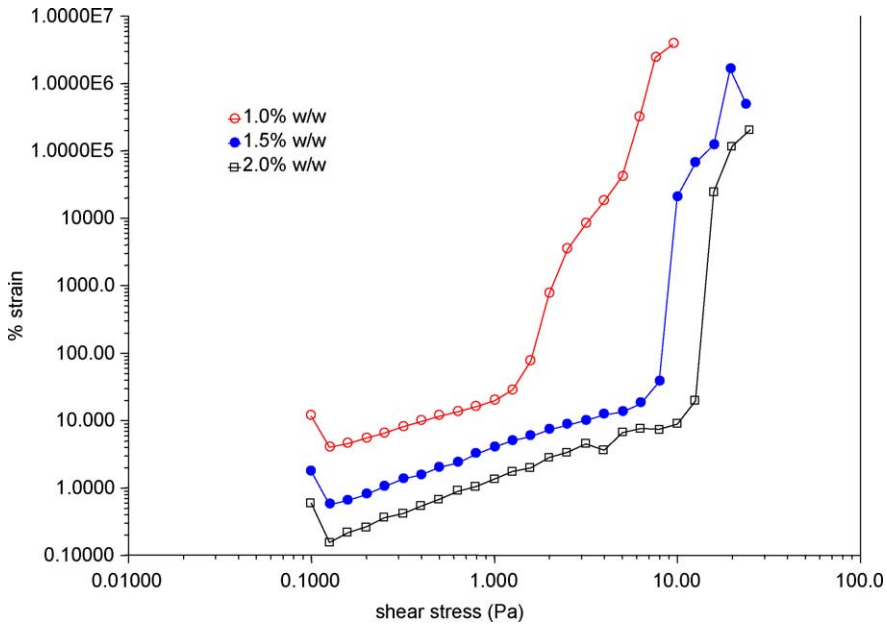

Fig. 7. Effect of shear stress on the resulting strain of hydrogels (Formula A) of varying concentration.

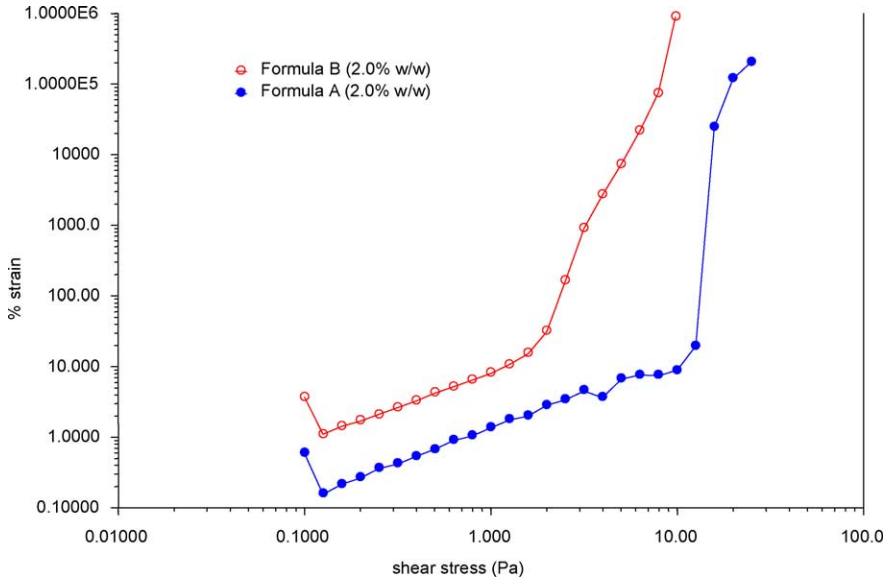

Fig. 8. Yield stress characterization of different grades of MCC/NaCMC hydrogels.

creased floc formation which in turn traps more of the continuous phase, which is purified water in this case.

In order to show that the gels are thixotropic, the MCC/NaCMC gels of varying concentration were subjected to a constant shear stress of 15 Pa over a period of time and the resulting viscosity was recorded. The data are presented in Fig. 6.

As evidenced from the data, the gels at 1.5% w/w and 2.0% w/w showed a decrease in viscosity over time and the 1.0% w/w gel did not exhibit any structure under the conditions tested. The lack of evidence at 1.0%

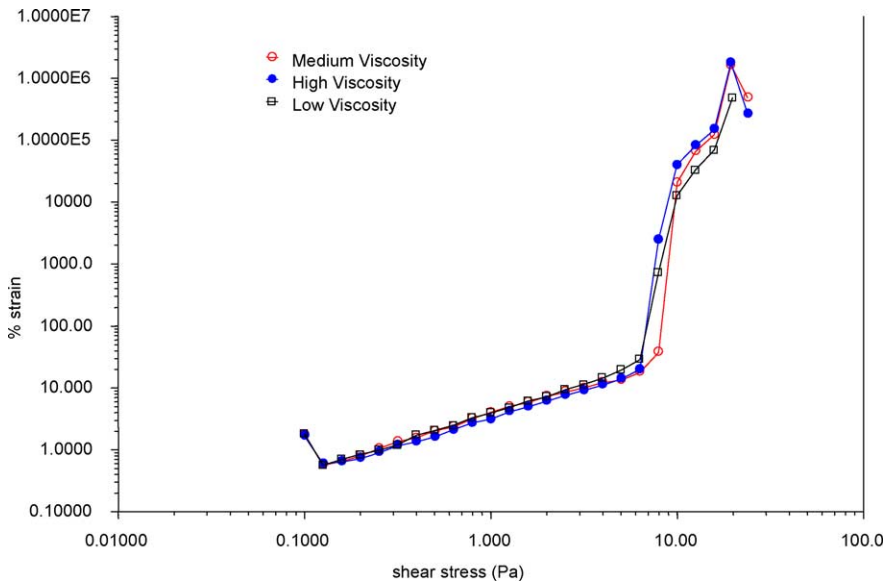

Fig. 9. Effect of lot to lot variability on MCC/NaCMC hydrogel (Formula A, 1.5% w/w) rheology in terms of yield stress.

w/w concentration may be due to the use of excessive shear stress or due to the lack of structure at that concentration. This will be investigated further in the future studies using oscillatory testing.

6.2. Yield stress of MCC/NaCMC hydrogels

Thixotropic gels build structure during rest and possess viscoelastic properties. From the shear thinning flow curves it was established the MCC/NaCMC gels do have yield stress. Yield stress is best described as the stress below which there is no real macroscopic flow in the material. The material behaves as an elastic gel under small stresses and strains below its yield stress value.

The yield stress data for Formula A hydrogels at varying concentrations indicate that the yield stress was directly proportional to the concentration of the gel (Fig. 7, Table 2). Formula B hydrogel (2.0% w/w) had significantly low yield stress value (1.2 Pa) when compared to Formula A hydrogel (10 Pa) of similar concentration (Fig. 8). The low yield stress could be attributed to the composition of Formula B, which is composed of a different grade of NaCMC and has a lower concentration of MCC particles when compared to Formula A.

Three different lots of Formula A with varying viscosity (35–88 cps) were obtained from the vendor and evaluated for yield stress at 1.5% w/w concentration (Fig. 9). All the three lots exhibited similar flow with a yield stress of approximately 6 Pa. The viscosity information provided by the vendor was generated using a Brookfield viscometer. The method used by the vendor (FMC) is highly subjective and the resulting data should be interpreted with caution.

Rheology studies on creams containing Formula B were shown to be important in characterizing the dependence of the viscoelastic parameters on the phase volume of the excipients, and thereby the stability of creams. The rheological characterization could also be considered for future regulatory guidance in addition to current tests for drug release to estimate stability of gel formulations (Adeyeye et al., 2002). Current results also identify the importance for hold time after manufacture, for structure build up which could be critical, in process development.

Table 2
Yield stress of MCC/NaCMC hydrogels of varying concentration—conventional viscometry

Formula A[a] concentration (% w/w)	Yield stress (Pa)
1.0	1.2
1.5	6.3
2.0	10.0
Formula B[a] (2.0% w/w)	1.2

[a] Formulae A and B differ in the quantitative composition of MCC and contain different grades of NaCMC.

7. Conclusions

Initial studies conducted on the samples showed the MCC/NaCMC hydrogels were thixotropic and possessed a measurable yield stress. The hydrogels were found to be extremely shear thinning. Yield stress studies showed that it takes approximately 1 week for the gel to build its structure after manufacture, and the structure was maintained for as long as 3 months. Different grades of MCC/NaCMC showed significantly different rheological properties that could be attributed to the difference in composition of the Formula B hydrogel. Dynamic oscillatory testing provided useful information about the rheological behavior of the Avicel hydrogels. The cause for thixotropy in MCC/NaCMC hydrogels will be further investigated based on the findings from the current study.

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